

EXHIBIT 4

**UNITED STATES DISTRICT
COURT NORTHERN DISTRICT
OF OHIO EASTERN DIVISION**

**IN RE: NATIONAL PRESCRIPTION OPIATE
LITIGATION**

This document relates to:

*Jennifer Artz, et al. v. Endo Health Solutions Inc.,
et al.*

Case No. 1:19-OP-45459

Michelle Frost v. Endo Health Solutions Inc. et al.

Case No. 1:18-OP-46327

MDL No. 2804

Case No. 17-md-2804

Judge Dan Aaron Polster

Expert Report of Christina A. Porucznik, PhD, MSPH

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I. Qualifications and Background

I, Christina Porucznik, PhD MSPH, completed my graduate training in epidemiology at the University of North Carolina School of Public Health in Chapel Hill, NC. I have been a member of the faculty at the University of Utah School of Medicine since 2005 and am an Associate Professor with Tenure in the Department of Family and Preventive Medicine, Division of Public Health.

I began researching harms related to drugs in 2004 and, since then, have published 15 papers in this area of the scientific literature. I have been a speaker at conferences and national meetings, consulted with several state governments through the National Governors Association on this topic, and served on the expert panel for development of the 2015 Centers for Disease Control and Prevention's Opioid Prescribing Guidelines for Chronic Pain. My research has explored characteristics of drug overdose decedents compared to other opioid users; the impact of changing regulations on opioid prescribing and subsequent harm; and uses of administrative data – including prescription drug monitoring program data – to study the problem of drug-related harm in the community. I have received research funding to support this topic area from the Robert Wood Johnson Foundation, the National Institute of Drug Abuse, the Utah Department of Health, and the Centers for Disease Control and Prevention.

My other area of research pertains to measuring environmental exposures during pregnancy and around the time of conception. This work directly informs the way in which I evaluate exposure assessment and reinforces the importance of exposure timing, dose, and duration on the eventual outcomes for the fetus and mother. A true and correct copy of my current curriculum vitae is attached as Exhibit A.

II. Scope of Report

The goal of this report is to present my summary of the state of the epidemiologic evidence regarding neonatal abstinence syndrome (NAS) in the United States. The primary focus will be on difficulties of exposure assessment, outcome assessment, and heterogeneity of the populations at issue (exposed pregnant women and the babies born to them). I understand that McKesson Corporation and other defendants in the litigation may use my expert report in opposing class certification. The opinions in this report are held to a reasonable degree of scientific certainty and are based on my education, training, professional experience, and review and working knowledge of the published literature on the relevant subject areas.

III. Summary of Opinions

Based on my experience as an epidemiologist, including my work on opioids and my work with exposure assessment during pregnancy, as well as on my analysis of the currently available literature on NAS, I conclude that numerous factors affect whether an infant experiences symptoms of NAS when exposed to opioids *in utero*, which symptoms are experienced, whether NAS is diagnosed in that infant, and the subsequent impact, if any, on growth and development.

In particular, challenges with assessing maternal exposure to a variety of substances during pregnancy, the purpose, timing, dose and duration of such exposures, and the heterogeneity of NAS assessment and treatment around and immediately after birth preclude a meaningful description of an identifiable class. Moreover, a variety of environmental and medical factors experienced after birth impact the long-term development of all children, including children diagnosed with NAS at birth. Finally, the scientific literature at this time demonstrates that there are inconsistent findings regarding long-term developmental harm attributable to *in utero* opioid exposures or NAS. To the contrary, studies to date have been mixed with variable results depending upon the design of the study, the exposure assessment paradigm, the age at which the children are assessed, the types of measurement tools used, and the developmental target being assessed.

IV. Analysis

A. Background

NAS encompasses a set of symptoms experienced by infants exposed to a wide range of substances *in utero*, some, but not all of which, are opioids. In addition, some opioids are used pursuant to a legitimate prescription and some are used illicitly. Other substances that may cause NAS include benzodiazepines like Xanax®, stimulants like Ritalin® or Adderall®, or street drugs like heroin or cocaine. At the time of diagnosis, hospitals often cannot and do not identify the exact drug or class of drugs causing NAS. Moreover, many infants have been exposed to multiple substances that may have contributed to the NAS symptoms being experienced. For example, researchers using Tennessee Medicaid data found that in women using multiple substances during pregnancy, including opioids, the use of benzodiazepines was associated with higher risk of NAS requiring pharmacological treatment. Using data from West Virginia, researchers identified variations in the incidence rate of NAS by hospital and NAS rates did not mirror substance exposure rates. West Virginia implemented a case definition for NAS that includes withdrawal from many substances, not just opiates, and is not limited to infants requiring treatment. As a result, not all infants with NAS have been exposed to opioids *in utero* or have their symptoms been caused exclusively or even in part by opioids. Nor do all infants exposed to opioids *in utero* experience NAS, particularly if the exposure is earlier in pregnancy.

The use of prescription opioids during pregnancy is not contraindicated and, subject to the clinician's judgment, may be the optimal treatment for the patient and her fetus. As with any prescription, there should be a discussion of risks and benefits for fully-informed, shared decision making. For example, some pain relievers are contraindicated in pregnancy, such as common non-steroidal anti-inflammatory pain relievers (e.g. ibuprofen, naproxen), because of known associations with birth defects or pregnancy complications, including miscarriage. A longitudinal study in a large commercial insurance database found that 14% of pregnancies include a prescription for at least one opioid medication with hydrocodone and codeine as the most common substances (Bateman, 2014). Most of these prescriptions were of short duration. Opioids are prescribed in pregnancy for a variety of pain conditions such as low back pain, abdominal pain, migraine, and fibromyalgia, as well as following surgical procedures and in cough medications.

That being said, women who are prescribed opioids during pregnancy have a variety of characteristics that are statistically distinct from those who are not: Patrick, 2015 (Pediatrics) reports that women prescribed opioids during pregnancy were of different races, but more likely to be white (72.4% compared to 65.8%), have anxiety disorder (4.3% compared to 1.6%), have depression (5.3% compared to 2.7%), have musculoskeletal disease (23.7% compared to 5.8%), experience headaches or migraines (8.3% compared to 2.0%), use tobacco (41.8% compared to 25.8%) and be prescribed an SSRI in late pregnancy, within 30 days of birth (4.3% compared to 1.9%). All these comparisons of women prescribed opioids during pregnancy compared to women not prescribed opioids during pregnancy were statistically significant at $p < 0.001$. Having a mother with depression or anxiety disorder, a mother with persistent pain conditions like musculoskeletal disease or migraine, or a mother who smokes are all situations that may affect the development of an infant. The importance of the diversity of the women who are prescribed opioids during pregnancy, and the diagnoses behind those prescriptions, is that these different characteristics — and other exposures associated with these characteristics — generate heterogeneous impacts on their children.

B. Pre-Birth Considerations

Growth and development during gestation is faster than at any other time in an individual's life. Dose, duration, and frequency of exposures during gestation generate different effects depending on the stage of gestation during which they are experienced. For example, insufficient folic acid in the first weeks post-conception is associated with increased risk of neural tube defects because the neural tube is forming during that time. The heart is formed and begins to beat around day 21-22 of development. Exposures before or during that time are more likely to affect heart development than later exposures. The brain develops throughout gestation, and therefore exposure assessment in pregnancy must consider the complete time period and all exposures rather than any single point exposure. It is well-recognized that developmental outcomes depend not only on exposures during gestation, but also on recognition and treatment of NAS, if present, the impact of confounding variables such as nutrition during pregnancy, quality of prenatal care, socioeconomic status, medical complications of the pregnancy and birth, maternal mental health and trauma experience, parenting or child-rearing quality.

I. Timing, Amount, and Duration of Exposure to Opioids

The quantity of exposure to opioids *in utero* along with the timing and duration of that exposure has significant impacts on a newborn's likelihood of developing NAS, as well as on the severity and longevity of NAS when experienced. The concepts of timing, dose, and duration of each substance used during pregnancy are of research interest, but the specific impact of each variable has not yet been well-described in the NAS literature because of poor ability to ascertain precise exposure assessment. (I note that I am aware of no literature assessing any relationship between a mother's use of opioids outside of pregnancy and the effects on a child.) However, in a related field, fetal alcohol spectrum disorder, the dose-timing issue is recognized as critical. Mattson, 2011 has summarized these challenges, which are equally applicable to NAS:

One of the biggest challenges in understanding the considerable variability of neurobehavioral outcomes of prenatal alcohol exposure involves identifying the dose and pattern of alcohol consumption as well as developmental timing of

exposure. In general, the amount of alcohol consumed is correlated with the severity of outcome (e.g., Sood et al., 2001; Streissguth, Sampson, & Barr, 1989). However, pattern of alcohol exposure can often moderate these effects, with binge-like exposures resulting in more severe deficits than chronic exposure (Bailey et al., 2004; Bonthius, Goodlett, & West, 1988). Timing of exposure is also important. Alcohol exposure during different periods of fetal development can greatly influence the pattern and severity of structural and functional abnormalities (Guerri, Bazinet, & Riley, 2009). Unfortunately, this level of detail is often difficult to document, particularly in retrospectively recruited samples, and individual studies provide varying degrees of detail concerning levels and patterns of exposure. However, although criteria used to delineate heavy prenatal alcohol exposure may be inconsistent across studies, these samples generally include children of women who meet criteria for alcohol abuse and dependence (e.g., Coles et al., 1991; Mattson, Riley, Gramling, Delis, & Jones, 1998; Mattson et al., 2010). Prospectively recruited samples, by design, allow for a greater precision when describing dose, pattern, and timing effects of prenatal alcohol exposure, but exposure levels are generally lower than in retrospective samples. (Mattson, Crocker et al., 2011).

Thus, to determine whether an opioid or any particular substance caused an infant's NAS, examination of the time, amount, and duration of exposure are critical. Determination of these three variables is challenging, but it is important to acknowledge that not every baby with NAS arrived at the diagnosis from the same exposure pathway, and our ability to separate the pathways is limited by imprecise measurement of drug exposures at the individual level. It may seem straightforward to obtain a record of opioid medications prescribed to a pregnant woman and use the infant's date of birth and estimated gestational age at birth (based on ultrasound and/or maternally-reported last menstrual period) to estimate when in pregnancy the exposure occurred. This estimation may result in misclassification of exposure in amount, resulting in both over- and -under-exposure estimations, as well as errors in the timing of exposure and failure to include other relevant substances. For example, if a pregnant woman receives an opioid prescription in early pregnancy, she may or may not fill that prescription. If she fills the prescription, she may or may not take all of the medication as prescribed. If one assumes that she took it as prescribed when she did not, then the estimate of early pregnancy opioid exposures (usually calculated in morphine equivalents) would be too high. If she did not take the medication as prescribed or use the entirety of the prescription, then the medication could still be available for her to use later in the pregnancy or during breastfeeding. She might also have had a smaller exposure in early pregnancy (when she took part but not all of the medicine) and then another exposure in later pregnancy when she took more of the medication. The exposure assessment based on her prescription history could not capture this pattern of use accurately. These scenarios do not even consider whether or not the woman is using other medications (prescribed or over-the-counter), opioids from other sources (whether misused prescription medications or illicit), other prescription drugs, or other drugs of abuse, alcohol, or tobacco. Given the potential impact of drug exposure on the developing brain, each of these potential exposures needs to be measured not just for the dose but also for the timing during pregnancy and inclusion in mixtures of exposures in order to ascertain the relationships with long-term development.

The type of opioid and the purpose of the prescription, if any, is another aspect of maternal heterogeneity that impacts variation in NAS incidence. Patrick, 2015 (Pediatrics) addresses this point. The authors there studied administrative claims data from the Tennessee Medicaid Program to identify maternal characteristics associated with opioid exposure and predict NAS presence in babies (Patrick, Dudley et al., 2015). They reported that 65% of the infants diagnosed with NAS in this dataset were born to mothers with one or more opioid prescriptions during pregnancy – for the other 35%, the opioid source was unidentified. Among women with at least one opioid prescription during pregnancy, NAS was more likely when the exposure was to maintenance opioids (29.3% of NAS cases), which constituted 2.7% of opioid prescriptions, compared to long-acting medications (14.7% of NAS cases), which constituted 0.6% of prescriptions, and the short-acting medications (1.4% of NAS cases), which constituted 96.2% of prescriptions. In this study, 96.2% of the opioids identified as being prescribed to pregnant patients accounted for only 1.4% of NAS cases, demonstrating that the overwhelming majority of prescriptions for opioids to pregnant patients are properly prescribed and used safely without resulting in NAS.

2. Treatment Programs

Whether a pregnant woman who has been given an opioid prescription during pregnancy is in a substance abuse treatment program and, if so, how she is being treated, are also important considerations in evaluating the likelihood and severity of NAS, as well as its cause. Experts agree that opioid-dependent women who are pregnant or become pregnant should remain in maintenance programs. Opioid maintenance therapy results in better infant and maternal health than illicit opiate use, with some therapies having better outcomes than others. Evidence suggest babies born to mothers being maintained on buprenorphine have lower incidence of NAS than babies born to mothers maintained on methadone. For example, in a double-blind, double-dummy, flexible-dosing, randomized, controlled study comparing methadone maintenance to buprenorphine maintenance, the same proportion of babies required treatment for NAS in each group, but babies exposed to buprenorphine required less pharmacologic treatment (89% less morphine) and spent less time in the hospital (10.0 days compared to 17.5 days) than babies exposed to methadone (Jones, Kaltenbach et al., 2010). As another example, early developmental data from a subset of participants from a randomized trial comparing opioid treatment regimens during pregnancy (n=39) demonstrated that buprenorphine-exposed infants had better neurobehavioral scores in the first month of life and less severe withdrawal than methadone-exposed infants (Coyle, Salisbury et al., 2012).

3. Exposure to Other Substances or Combinations of Substances

The effects of exposure to opioids on the developing fetus are modified by exposure to other substances, concurrent or not. For example, in Patrick, 2015 (Pediatrics), discussed above, the authors performed modeling with the exposure and demographic data available to them and found that NAS increased with longer duration of opioid exposure, numbers of cigarettes smoked per day, and prescription for an SSRI in the last 30 days of pregnancy. Another analysis of Tennessee data found that benzodiazepine exposure was associated with higher risk of NAS requiring treatment among infants exposed to multiple substances including opioids. Thus, the opioid type or possession of a single prescription alone were not the only factors that affected

NAS rates. Maternal smoking and use of other medications (SSRIs) was also associated with increased NAS. Although this study was retrospective and based on claims data in one state's Medicaid program, the study evaluated available data on over 100,000 pregnancies. Other studies have found abuse of opiates is associated with polydrug use and problematic alcohol use.

Like determining timing, dose, and duration of exposure to opioids *in utero* is difficult, accounting for the various alternative substances each individual in the proposed class has been exposed to will also prove challenging and require an individualized assessment. Moreover, determining exposure to other substances is not the end of the inquiry. An additional individual-level exposure assessment is required to determine the contribution of prenatal opioid exposure to a subsequent NAS diagnosis in light of the birth mother's exposure to other substances. Making things more challenging, existing studies of opioid exposure during pregnancy and incidence of NAS have noted the difficulty in accounting for exposure to various alternative substances because of measurement difficulty and sample size issues. Simply put, not enough women in these studies were exposed to the same substances to make assessable and meaningful exposure categories. As a result, the actual exposure assessed in these studies may have been heterogeneous – some women only were exposed to prescription opioids in the course of medical care while others ingested not only prescribed opioids but other substances as well. In this scenario, assigning the burden of causality to a component of the exposure is nearly impossible, and certainly unwise.

C. At Birth Considerations

NAS diagnosis is dependent upon not only recognition of the clinical signs and symptoms of the syndrome in a newborn, but also the clinical suspicion that the symptoms may be caused by withdrawal and not some other cause, such that the diagnostic steps are initiated before the infant leaves the hospital and continued for sufficient time to complete the diagnostic protocol for NAS.

1. Differences in Hospitals' Diagnosis of NAS

There is not an agreed-upon clinical assessment for NAS. As a result, hospital-related differences affecting NAS diagnosis rates and treatment have been noted. These differences were highlighted in a study of methadone treatment during pregnancy in which the opioid-exposed mothers delivered at eight different hospitals. (McCarthy, Leamon et al., 2015) The proportion of babies treated for NAS differed by hospital with two hospitals at 33% and another only 12%.

Clinical suspicion and diagnosis of NAS at the hospital level can vary based on patient-level factors, system-level factors, and social factors. Without a standard protocol and case definition, we cannot be sure that reported incidence rates represent similar situations or babies. The initial presentation of NAS, which may begin within a day or as late as 10 days following birth, includes a wide range of non-specific and subjectively-assessed symptoms (including but not limited to sleep problems, high-pitched crying, tight muscle tone, irritability, and poor feeding) that may be caused by NAS or other reasons. A reason to suspect *in utero* substance exposure is critical to diagnosis. Many mothers leave the hospital within 24 to 48 hours after delivery, possibly before NAS symptoms begin. Without reason to keep the mother-child dyad so that

repeat evaluations can be completed with the Finnegan or other scoring system, a baby will not be diagnosed with NAS. Therefore, a hospital with routinely quick discharge might be less likely to diagnose NAS. If hospital staff are trained in a facility with high rates of NAS diagnosis, they might bring their clinical suspicion with them to a new facility and change the rate of diagnosis in that facility through their implementation of practice patterns. In a community with a known high rate of substance use, there may be more clinical suspicion of NAS and usual procedures might be more likely to be established so as to not miss potential NAS cases.

When researchers compared various data sources for NAS surveillance in Tennessee, a state which has been heavily affected by substance abuse, they found stark differences in the NAS capture rates from the different data sources, with only about half of the babies identified in both data sources. This was a comparison of an intentional surveillance system for NAS [Tennessee NAS Public Health Surveillance System (TNSS)] with hospital discharge data and illustrates the variation in the way that NAS is measured even within a single state. Similarly, hospital-level characteristics (urban/rural; teaching/non-teaching) have been associated with different rates of identification of maternal opioid use disorder and NAS in a study of rural residents using the National Inpatient Sample with variation among sociodemographic and clinical characteristics associated with the diagnoses by hospital type as well.

2. Patient-Level Factors: Birth Mother's Condition During Birth

If a woman presents to the hospital in labor and apparently under the influence of one or more substances, it would be likely for biological samples to be collected and analyzed for toxicology. If drugs are present, then the suspicion that the baby may experience NAS would be higher than a baby born to a mother who did not arrive at the hospital under the apparent influence of substances. However, that second mother could have used substances during her pregnancy that might result in NAS. If she did not disclose her drug use and there was no clinical reason for toxicology testing at delivery, her baby's NAS might be missed. Given the evidence that not all babies exposed to substances *in utero* will develop NAS, this variation in potential diagnosis based on differences in maternal condition or disclosure of substance use enhances the heterogeneity within this population and weakens the ability to ascertain an identifiable class of babies diagnosed with NAS after *in utero* exposure.

D. **After Birth Considerations**

Every exposure following birth contributes to infant and child development. Exposures experienced during hospitalization, such as medications, may be assessed by means of medical record review. Exposures once babies leave the hospital, however, are numerous and probably impossible to assess with any degree of completeness. Every aspect of nutrition, home environment, social relationships, and life experiences affects child development, and yet measuring the individual variation and heterogeneity of these exposures is not feasible.

1. Heterogeneity of Treatment of NAS

How a child was treated for NAS is another individualized factor that impacts the long-term outcome for each child. Treatment for NAS is known to vary depending on the NAS symptoms, family situation, hospital type, and geographic region. Treatment for NAS is also applied

differentially from care-provider to care-provider, based on several criteria, many of which are subjective. Treatment for NAS varies from comfort-only care to pharmacological treatment with morphine or other drugs. Logan 2013 suggests that 50–70% of infants require pharmacological treatment. Whether pharmacological treatment is required is “...affected by genetics, other drug exposures, gestational age, breastfeeding, and rooming-in.” (Logan, 2013). However, continuing exposure to opioids to manage withdrawal after birth may contribute to long-term consequences for infants with NAS. Because of the lack of standard treatment protocols, it is difficult to account for the impacts of different types of treatment and separate the effects of the *in utero* opioid exposure that led to the development of NAS from the effects of treatment. Research has thus far been unable to separate developmental impacts of NAS treatment from the exposures that led to the NAS diagnosis.

2. Home Environment

It is well-recognized that a child’s home environment impacts their academic and neurodevelopmental outcomes. The factors are numerous and diverse, including but not limited to: socioeconomic conditions, nutrition, access to education, parental relationships, family unit status (natural parent, foster care, adoption), exposure to violence, abuse, or neglect, exposure to substance abuse (parents or children), and environmental exposures (chemicals, smoking, lead, etc.).

In the recent review by Conradt et al (2019), only two of the included studies were able to control for foster care placement as a confounding factor that could impact the potential relationship between prenatal opioid exposure and developmental outcomes. One study even used the number of foster care placements as a variable in the analysis. This highlights a challenge with measuring the child-rearing environment, particularly in foster care, in that complete exposure assessment may not be possible for each home or environment in which an infant or child resides. Home-level characteristics, such as presence of lead paint or proximity to a highway, also affect developmental outcomes; and for children raised all or partly in foster care, it would not be feasible to measure each environmental variable. For example, by definition, infants taken from their mothers are likely to be fed artificial milk rather than human milk. This nutritional (artificial milk vs. human milk) and care-giving difference (attachment aspects of bottle-feeding vs. breastfeeding) inherent in foster care will also affect child development.

3. Parenting Impacts

The quality of parenting immediately after a child is born will affect the long-term impacts of NAS. For example, it has been suggested that mothering-related factors such as breastfeeding and rooming-in may affect NAS treatment and outcomes. However, selection biases and confounding may account for the observation that babies who are breastfeeding have less severe withdrawal, and require shorter NAS treatment and less medication (Logan, 2013). Mothers who are well enough and organized enough for breastfeeding and rooming-in are likely different than mothers not deemed fit enough for these experiences, and have likely had different drug exposure experiences during pregnancy as well. When compared to the Merhar 2018 study in which few babies left the hospital with their mothers, the suggestion that maternal characteristics and behaviors matter is enhanced. In that study, no babies who began foster care were with the

mother at age 2, and children raised in foster care scored higher on cognitive tests but not in any other metric, illustrating how parenting may have variable effects on early development.

4. Other Environmental and Medical Risk Factors

Previous studies about long-term outcomes among babies exposed to substances *in utero* acknowledge that these babies are also likely raised in high-risk environments by mothers who were likely raised in high-risk environments themselves, and it is difficult to impossible to separate the effects of *in utero* chemical exposures from effects of the social-environment (Lester and Lagasse, 2010). Logan 2013 specifically calls out the importance of characterizing environmental risk factors when evaluating pediatric outcomes following NAS:

Potential long-term effects of prenatal methadone exposure on infant and toddler development are not known, primarily because of the scientific issue of isolating independent effects of methadone, comorbid substance exposure (e.g., alcohol, tobacco, other illicit drugs) and environmental and medical risk factors (e.g., low socioeconomic status, poor prenatal care, severity and treatment for NAS).

(Logan, 2013). It is well-recognized that children experience many exposures following birth that may affect long-term development. In the realm of environmental epidemiology investigating known neurotoxins such as mercury and lead, it is the preferred practice to include biological exposure assessment of the child at multiple time points in addition to measures of *in utero* exposures because there is broad agreement that exposures following birth cannot be disregarded in the study of development.

E. Literature on the Impacts of NAS

1. Long-Term Developmental Impacts

The long-term impacts of opioids exposure *in utero* on child development are uncertain and variable. A recent article by Conratt, et. al (2019) cites the difficulties of exposure assessment during pregnancy, heterogeneity of exposure, and heterogeneity of treatment as reasons contributing to the current lack of data concerning developmental impacts (Conratt, 2019). There are also differences in outcome depending upon the age of assessment, type of assessment (e.g., I.Q., cognition, aptitude, etc), the types of tools used to measure outcome, the location and type of facility doing the testing, the purpose of the testing, etc.

A recent study of early childhood outcomes within the Pennsylvania Medicaid program compared children in three groups: (1) with *in utero* exposure to opioids, (2) with *in utero* exposure to tobacco, and (3) no exposure. The study found similar probability of complex chronic condition diagnosis among all three groups. These findings were consistent when repeated among children with identified neonatal opioid withdrawal syndrome.

Few studies have reported on the developmental outcomes of babies treated for NAS. Among those few studies, significant flaws limit the impact of their findings. For example, Merhar 2018 (J. Perinatol) is one of the few studies that has attempted to examine the developmental outcomes of babies treated for NAS (Merhar, 2018). It was a small study (n=87) in which examiners

performed the Bayley assessment on children at age 2. The Bayley assessment is a systematic observation of play tasks used to gauge development with the aim of monitoring development (if administered repeatedly), identifying developmental delay, and/or supporting child-specific interventions. Children who had been treated for NAS scored worse than the norm (*but still in the normal range*) on this assessment on all scales. Limitations of this study include poor follow up. The authors initially identified 455 patients treated for NAS and then seen in their follow up clinic, but only performed the Bayley assessment on 102. The Bayley examiner was not blinded to the child's diagnosis — leading to possibilities of interviewer bias. Notably, in this study the majority of children did not leave the hospital in the care of their mothers — 44% into foster care or adoptive family, and 30% with father or another relative. There was no attempt to account for parenting or household situation in the first two years of life and how that might relate to the findings. Bayley scores were not associated with: type of treatment for NAS, maternal polysubstance use (as measured by urine toxicology at delivery) as compared to single substance use, length of hospital stay, gestational age, or birthweight. Thus, the authors' conclusion that children treated for NAS are developmentally different at age 2 than typical children is going too far given the data presented in this paper.

In contrast, a systematic review and meta-analysis of neurobehavioral outcomes following *in utero* exposure to opioids found only five studies that had quantitative measures of outcomes (Baldacchino, Arbuckle et al., 2014). Based on those five studies, the conclusion was that there were no significant impairment compared to non-exposed children. However, this assessment was based on a meta-analysis of five relatively small case-control studies and, given how much happens to children during the first five years of life, drawing strong conclusions about long-term outcomes from NAS is difficult.

To the extent plaintiffs suggest *in utero* opioid exposure causes autism or any neurodevelopmental condition that falls within the autism spectrum, the epidemiologic data demonstrate that the cause or causes of such conditions is highly individualized and fraught with confounders. For example, diagnoses of autism spectrum disorders are highly associated with genetics, maternal co-morbidities (e.g., depression), and external circumstances like birth spacing. Autism, like all neurodevelopmental conditions, is affected by innumerable factors that are specific to each child and their environment. The same is true with regard to common conditions like attention deficit disorder and attention deficit hyperactivity disorder. Plaintiffs' citation of Conner 2019, which focused largely on insurance type and did not control for any of these factors, is not to the contrary.

Opioids variably act on receptors in the brain, and it has been noted that the dose and timing of the exposure is critical as the windows of vulnerability are variable. This fact argues against the definition of a class of exposed babies — depending on the timing and dose of exposure, the potential impacts could be very different and dissimilar enough to refute the notion of a meaningful class. Plaintiffs' expert, Dr. Howard, notes that, "Current data cannot clearly differentiate between the long-term neonatal outcomes resulting from the prenatal use of prescription opioids, illicit drugs or opioid maintenance therapy." The status of poor exposure assessment in the literature and clinical practice demonstrates an inability to define a meaningful class with reasonable sensitivity and specificity.

2. Birth Defects

Evidence linking exposure to opioids in pregnancy with birth defects is limited and mixed. Some small studies report effects with some defects and others not. The most that can be said for the literature on birth defects is that there are numerous types of birth defects, most of which are associated with genetics or a variety of different exposures to different substances at different times. The ability to link opioid exposure to particular birth defects is minimal based on the available evidence.

F. Medical Monitoring

Despite the uncertainty of long-term developmental effects from prenatal opioid exposure, plaintiffs' experts have suggested development of a registry for prospective surveillance of potentially affected infants as they grow and develop. Enrollment in such a monitoring system has the potential to create harm for the children. If they have been labeled as 'NAS babies,' then there is a risk that their opportunities will be limited because of expectations for developmental difference which may become a self-fulfilling prophecy. If these children are subject to placement into a certain educational track because of their membership in a registry, they may be harmed compared to their peers who had similar exposure but were never enrolled or whose family refused enrollment in prospective monitoring. Additionally, there is the potential that such a registry could create problems for the children in the future. For example, registry membership may make obtaining healthcare for these children difficult, more expensive, or impossible. It is possible that labeling children and enrolling them in such a medical monitoring program without scientific evidence of benefit could actually result in more harm than benefit to the monitored children.

In addition, there are certainly ongoing research and quality improvement efforts to collect data about the developmental experience of children exposed to opioids *in utero* with the eventual goal of improving treatment for exposed babies. A search of PubMed for 'surveillance neonatal abstinence syndrome' (conducted by CP on 2/20/20) identified steady publication in this area with 31 records for 2016; 37 records for 2017; 56 records for 2018; and 34 records for 2019. Given the timing of the identified increases in opioid prescribing in the United States, exposed children are now reaching ages at which researchers may be able to assess development effects; however, the exposure assessment for these children will be variable and limited to whatever records were collected years ago during their mothers' pregnancies. Prospective studies with strong exposure assessment during pregnancy and assessment of the child at multiple timepoints would provide the strongest evidence, but these are not represented in the literature.

I reserve the right to amend or supplement this report and my opinions based upon new or later acquired facts, literature or information. My hourly rate is \$350 and I have not testified in deposition or trial in the last 4 years.

Date:

2/21/20


Christina A. Porucznik, PhD, MSPH